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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,867	09/13/1999	DAVID A. WILLIAMS	7037-377/IU-	5039

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/394,867	Williams
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 12, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11-23, 38-43, and 79-83* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11-23, 38-43, and 79-83* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Sep 13, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January November 12, 2002 has been entered as Paper No. 18.

Claims 2-37, 44-78, 84-93 have been canceled, claims 38 and 82 have been amended by the amendment dated Nov. 12, 2002.

Elected claims 11-23, 38-43, 79-83, to which the following grounds of rejection remain applicable, are pending.

The drawings are objected in view of the reasons set forth in the PTO-948 attached to this office action. In order to facilitate the publication of a patent should this application be issued as a US patent, Correction of the drawings before the notice of allowance is suggested.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-43, readable on a genus of amino acid sequences referred as a "first amino acid sequence", which must exhibit a binding activity as claimed, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention.

The specification and the state of the prior art only describe and provide sufficient description of SEQ ID NOS 1 and 2, functionally active fibronectin and fibronectin fragments that retain the claimed biological function, *e.g.,* the binding activity of the CS-1 domain of fibronectin ad of the heparin-II binding domain of fibronectin.

Applicant's disclosure of one species of a functionally active fibronectin does not provide sufficient description of the specific structures of a representative number of unspecified protein sequences other than functionally active fibronectin peptides that would support applicant's possession of the genus of amino acid sequences which must possess the claimed biological activities. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, *e.g.* genus of similar amino acid sequences and/or unspecified amino acid sequences with the required properties as recited in the claim, requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays identifying the "agents"; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of therapeutic nucleic acid reagents.

It is not sufficient to support the present claimed invention by disclosing simply functionally active fibronectin because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other amino acid sequences as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming all amino acid sequences that must possess the biological property as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear

depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of "amino acid sequences" as claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Should the claims be amended to replace the " a first amino acid sequence" with -- a fibronectin, a fibronectin fragment, or mixture thereof, the stated above rejection will be withdrawn by the examiner.

Applicant's response (pages 6 and 7 of the response filed September 20, 2001) has been considered by the examiner but is not found persuasive for the reasons set forth in the stated rejection and for the following reasons:

In response to applicant's assertion (the response, pages 3 through 7) that the disclosure is sufficiently described so as to enable one skilled artisan to practice the full breadth of the invention as intended, that the defined fibronectin polepeptides, fibronectin fragments, and close analogs are fully described in the present application, *e.g.,* citing pages 5, 6, 15-18 from the specification, and that biotechnology art is routine with respect to the use of mutation and/or deletion assays to determine a variant of a known polypeptide and yet retaining the biological function of the know polypeptide, is sufficient to reasonably convey to a skilled artisan that applicants had possession of the genus claim of the polypeptide, applicant's response is not found persuasive because of the reasons set forth in the stated rejection, and because the issue is not that applicant does not describe sufficiently on the basis of applicant's specification any fibronectin polypeptide, fibronectin fragment, and mixtures thereof. The issue is whether or not a skilled artisan would have recognized that the as-filed specification provides sufficient description of a representative number of species of proteins and/or fragments thereof, or analogs other than functionally

active fibronectin or fibronectin fragments. Neither applicant's response nor the cited pages of the specification provides any evidence to overcome the written description rejection. Note that "fibronectin, fibronectin fragments" are not recited in the rejected claims. The breadth of the claims embraces a genus of number of unspecified polypeptide sequences other than a functionally active fibronectin and yet the as-filed specification does not provide a sufficient description of a representative number of species of the claimed genus. The issue is not that the claims have to be restricted to a specifically named SEQ ID NO. encoding a fibronectin protein or fragment, nor is it that undue experimentation is lacking to discover functionally active fibronectin fragments other than the SEQ ID NO disclosed by the specification, but rather is the lack of sufficient description of the genus of unspecified amino acid sequences **other than functionally active fibronectin**, as generically claimed and clearly contemplated on the basis of applicant's specification.

Claims 38-43, readable on a genus of amino acid sequences that must exhibit the binding activities as claimed are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to fibronectin or fibronectin fragments that exhibit the binding activities as claimed.

The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all immobilized materials containing unspecified ligands, as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically and with respect to the claims, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended.

In addition, the application does not provide sufficient guidance and/or factual evidence to enable one skilled in the art to practice the invention directed to a method for increasing the frequency of transduction of all viable mammalian cells by a replication-defective retrovirus vector by using an effective immobilized amount of material other than active fibronectin fragments which encode Heparin II binding domains, nor is it apparent how one skilled in the art reasonably extrapolates from the disclosure including the exemplified *in vitro* data to the transduction methods as claimed, wherein an increase of retroviral transductions is affected by the presence of an unspecified materials, ligands, and/or polypeptides. Furthermore, it is not apparent how one skilled in the art determines without undue experimentation on the basis of applicant's disclosure as to which polypeptides other than active fibronectin polypeptides, *e.g.,* Heparin II binding domain and VLA-4 binding domain of fibronectin, increase the transduction of a retroviral vector into any viable mammalian cells including human pluripotent stem cells. Note also that Moritz *et al.* (J. Clin. Invest, 1994) teach that the underlying biochemical and molecular mechanism of fibronectin which affects the transduction efficiency of retroviral vectors into hematopoietic stem cells is not known. In addition, the application and claims contemplate that amino acid sequences similar to SEQ ID NO: 1 (encoding a Heparin II binding domain of fibronectin) and any amino acid sequence derived or obtained from collagen or fibroblast growth factors are also effective to increase transduction of retroviral vectors into any target cell. However, it is not apparent as to how one skilled in the art identifies and/or determines, without any undue experimentation, as to which "amino acid sequences" other than a functionally active fibronectin is effective for binding to a retroviral vector and affects a transduction efficiency of a retroviral viral vector into any viable mammalian cell. The problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can

be tolerated with respect thereto is complex and do not invariably follow empirical rules. Unpredictability is keyed on the fact that simple analysis of primary, secondary, tertiary, and quaternary structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable (see Ngo *et al.,* in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.,* (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Thus, one skilled in the art would have to exercise an undue experimentation to employ any polypeptides or ligands other than fibronectin for the purpose of enhancing retrovirus transduction in the a cell culture of viable hematopoietic stem cells.

For the reasons discussed above, it requires undue experimentation to practice the full scope of claimed invention as claimed, particularly given the breadth of the claims, the amount of undue experimentation necessary because of the absence of guidance and the lack of reasonable correlation between the data obtained from the working examples to the subject matter being sought in the claims, and the unpredictable nature of the art.

In response to applicant's assertion (pages 8 and 9 of the response) that sufficient guidance was provided by the specification to enable a skilled artisan to practice the full breadth of the claims, and that it is routine in the art to go to existing sequence databases to utilize close analogs for the practice of the claimed invention, the comments are not persuasive because of the reasons set forth in the stated rejection, and because the issue is not that the stated rejection attempts to restrict applicant's invention to just the disclosed SEQ ID NO encoding a fibronectin. Note also that it is the as-filed specification that must provide the essential materials which include sequences other than functionally active fibronectin fragments and yet has the same activity as a fibronectin protein for the practice of the full scope of the invention.

Claims 11-23, 38-39, 79-83 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lim *et al.,* PNAS, Vol. 86, pp. 8892-8896, 1989, taken with any of David A. Williams *et al.* (Blood Cells, 20, pp. 504-516, 1994, IDS), Moritz *et al.,* J. Clin. Invest. 1994, 93:1451-1457, Williams and Patel (US Pat No. 5,686,278) and Finer (US Pat No. 6051,427), and further in view of applicant's admission over the prior art of record on pages 16 and 23 of the as-filed application.

Lim *et al.* teach a method of grafting murine stem cells enriched in hematopoietic stem cells transduced by a replication defective retroviral vector expressing a human ADA gene for long-term expression of the ADA gene in mice transplanted with the cells (entire disclosure). Culture medium containing the transfected stem cells is also disclosed in the Lim *et al.* reference.

Lim *et al.* do not teach the concept of employing functionally active fibronectin, *e.g.,* FN 30/35 which contain both the binding domains as recited in the claims, to facilitate or enhance the transduction of retrovirus vectors into the cells.

However, at the time the invention was made, Williams, Moritz, Williams and Patel, and Finer *et al.* teach a method of obtaining retrovirus transduced blood stem cells comprising infecting the cells with a supernatant containing retrovirus vectors expressing a transgene on FN 30/35 coated dishes so as to enhance the infection efficiency (entire document, especially p. 510, Fig. 6, and p. 511). With regard to the use of other extracellular proteins including type IV collagen, Williams on page 510 teaches the method wherein collagen IV coated plates were employed to enhance the retrovirus infection. The Williams, Moritz, Williams and Patel, and Finer *et al.* references as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing the retrovirus infecting the stem cells, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

In addition, pages 16 and 23 of the as-filed specification teaches that functionally active fibronectin fragments including H-296 and CH-296 are available in the prior art of record.

It would have been obvious for one of ordinary skill in the art to have employed any fibronectin

fragments known in the prior art as long as the fragments contains the essential domains of the FN-30/35 in the grafting method and/or cultures and/or compositions of Lim *et al.* One of ordinary skill in the art would have been motivated to have employed fibronectin fragments including the FN-30/35, H-296 and CH-296 in the grafting methods and/or compositions of Lim *et al.* so as to increase the retroviral transduction into the stem cells, as taught by the Williams, Moritz, Williams and Patel, and Finer *et al.* references.

In addition, it would also have been obvious for one of ordinary skill in the art to not employ a co-cultivation step or retroviral producer cells because the Williams, Moritz, Williams and Patel, and Finer *et al.* references as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing a supernatant containing the retrovirus expressing a transgene and stem cells desired for retroviral transduction, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

Claims 11-23, 38-43, 79-83 remain rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a), as being unpatentable over either Williams *et al.* (US Pat No. 5,686,278), or Finer (US Pat No. 6,051,427).

Williams *et al.* and Finer *et al.* teach a method of obtaining retrovirus transduced blood stem cells including human stem cells or cord blood cells deficient in ADA comprising infecting the cells with a supernatant containing retrovirus vectors expressing a transgene, *e.g.,* ADA, on FN 30/35 coated dishes so as to enhance the infection efficiency (entire documents, especially columns 7-12 of Williams *et al.* and columns 41-44 of Finer *et al.*). The Williams *et al.* and Finer *et al.* references as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing the retrovirus infecting the stem cells, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

Absent evidence to the contrary, the methods, cultures and compositions of the references have all of the properties cited in the claims, or at least, in the alternative, would have been obvious over the

methods and compositions as claimed.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-23, 38-43, 79-83 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,686,278 or claims 1-14 of US Pat No. 6.033.907.

Although the conflicting claims are not identical, they are not patentably distinct from each other because all three sets of claims are readable on

A method for obtaining a transduced population of viable mammalian cells by a retrovirus expressing ADA, a composition containing the transduced populations, and a method of enhancing the transduction of retrovirus vectors into hematopoietic cells, wherein all of the methods and compositions require the presence of substantially pure fibronectin, substantially pure fibronectin fragments, or a mixture thereof, so as to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector.

Applicant's response indicating that an correction of inventorship will be filed to overcome all of the prior art rejections. However, insofar as the official response has not been filed for the examiner's consideration, all of the stated rejections remain for the reasons of record.

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER